American Chemistry Council Formaldehyde Panel

See attached comments from the American Chemistry Council's Formaldehyde Panel regarding Draft Identification of Priority Consumer Products: Safer Products for Washington Cycle 2, Phase 2, Formaldehyde and Formaldehyde Releasers in Cleaning and Household Care Products.

December 20, 2024

Safer Products for Washington
Hazardous Waste and Toxics Reduction Program
Washington State Department of Ecology
Olympia, WA 98504-7600

Submitted Electronically to: SaferProductsWA@ecy.wa.gov and Online Comment Form

RE: Draft Identification of Priority Consumer Products: Safer Products for Washington Cycle 2, Phase 2, Formaldehyde and Formaldehyde Releasers in Cleaning and Household Care Products

Dear Washington State Department of Ecology Staff,

The American Chemistry Council (ACC) Formaldehyde Panel (Panel)[1] appreciates the opportunity to comment on the Washington State Department of Ecology (the Department) Draft Identification of Priority Chemicals Report to the Legislature: Safer Products for Washington Cycle 2, Implementation Phase 2 (Draft Phase 2 Report). The Panel recommends that the Department fully consider the body of literature relevant to the hazards and risks of formaldehyde before finalizing its report. The available formaldehyde literature is vast and complex. Our comments highlight areas where the Department has failed to incorporate peer-reviewed science, government reports and other scientific evidence into its decision to propose formaldehyde and formaldehyde releasers in cleaning and household care products as a priority product for regulation under Safer Products for Washington. We also express our support for the comments submitted by the American Chemistry Council Center for Biocide Chemistries (CBC).

Formaldehyde is a naturally occurring substance, made of carbon, hydrogen, and oxygen. It is an ever-present part of our world, produced by every living organism – including humans, who make and process about 1.5 ounces of formaldehyde per person every day. It is a well-studied compound and, thanks to decades of innovation, has become a critical component used safely in everyday goods including automobiles and electric vehicles, wood products, medical devices, vaccines, fertilizers, and antimicrobials. Formaldehyde is an essential building block, and its versatile chemical properties make it a common and beneficial part of modern life. Products that are based on formaldehyde technologies have broad roles in the economy and are critical to the integrity of supply chains, supporting 987,000 jobs and $552.7 billion in sales in 2022 in the

[1] The Formaldehyde Panel's members include producers, suppliers, and users of formaldehyde and formaldehyde products, as well as trade associations representing important formaldehyde applications. More information is available at www.americanchemistry.com/formaldehyde.

United States.[2] Industries and sectors which rely on formaldehyde include housing; building and construction; food and agriculture; aerospace; science and preservation; semiconductors; automotive; national security; and medicine and medical technologies.[3]

Cleaning and household care products, including surface cleaners, disinfectants, and other household products, are essential for maintaining public health and hygiene. Preservatives, including formaldehyde-releasing antimicrobial chemistries, play crucial roles in ensuring the safety and sustainability of water-based products. We direct the Department to the CBC comments that outline the existing regulatory findings supporting the use of formaldehyde releasers in cleaning and household products and underscore the importance of preservatives and formaldehyde-releasing agents, and provide the rationale for why the use of formaldehyde-releasing chemistries should not be restricted.

Ensuring the safety of consumers and the environment is an important objective of Safer Products for Washington. To effectively accomplish this objective, the Department must prioritize chemical hazards demonstrated by the best available science and applications that present a real risk to consumers and the environment. The Panel offers the Department the following comments related to its proposed identification of formaldehyde and formaldehyde releasers in cleaning and household care products as a priority product under the Safer Products for Washington program. As a threshold issue, the Panel reiterates previous comments that many key studies and reviews regarding the risks presented by formaldehyde are not cited, described, or taken into account by the Department. In order to ensure that the Department's actions are consistent with the best available science and with the Department's statutory obligations, these studies and their conclusions must be included in the final report and in the Department's analysis of formaldehyde.

These comments include the following key points:

- Formaldehyde has unique properties that must be considered
- Formaldehyde is well studied and safe thresholds for exposure exist
- A threshold-like dose response exists for nasal tumor formation
- Lack of biological plausibility between inhaled formaldehyde and leukemia
- Typical formaldehyde exposures are not associated with asthma
- Observational studies are not best available science
- Controlled human exposure studies are the "gold standard"
- Consumer exposure to formaldehyde is low and adequately regulated
- Formaldehyde is currently being reviewed at the federal level
- Latest peer reviews and publications on formaldehyde should be considered

[2] ACC, Formaldehyde Producers Boost U.S. Economy, available at: https://www.americanchemistry.com/industry-groups/formaldehyde/benefits-applications.

[3] Summary descriptions of formaldehyde's essential role in each of these sectors are available at: https://www.americanchemistry.com/industry-groups/formaldehyde/benefits-applications.

1. Formaldehyde has Unique Properties that Must be Considered

While formaldehyde is considered to be a volatile organic carbon (VOC), it is not typical. Formaldehyde is naturally produced as a metabolic byproduct by all living organisms. At room temperature, formaldehyde is a colorless, flammable gas that has a distinct, pungent smell which is typically detectable above 1 ppm. Dermal contact to formaldehyde solutions at sufficient concentration can cause severe injury to the skin accompanied by drying, cracking, and scaling. Inhalation exposures have been extensively characterized in controlled studies with human volunteers, including asthmatics and other sensitive individuals, which provide a robust database from which a point of departure can be determined.

The kinetics of formaldehyde inside the body have also been well studied.[4] Formaldehyde is a normal product of intermediary metabolism in mammals, formed endogenously from serine, methionine, choline, and glycine by demethylation of N-, O-, and S-methyl compounds. It is present at concentrations near 0.1-0.2mM in blood and tissues.[5] Due to its high reactivity with water (it forms a reversible hydrate), formaldehyde is taken up readily into epithelial tissues as it passes through the nose and has a significant anterior to posterior concentration gradient along the nasal epithelium.[6] The nasal tissues already have a level of endogenous formaldehyde, and low concentration exposures are not expected to cause any appreciable increase above background. Additional dosimetry modeling has also explored whether exogenous formaldehyde can increase endogenous levels, and at doses up to 1.9 ppm the models showed that any increase in endogenous formaldehyde would be far below existing endogenous levels.[7] This important finding informs the biological plausibility of systemic effects.

2. Formaldehyde is Well Studied and Safe Thresholds for Exposure Exist

Formaldehyde's unique chemistry, including the fact that it does not follow Haber's Law, meaning that the incidence and severity of a toxic effect does not depend on both the exposure and duration, must be appropriately weighed and considered when looking at the best available science to inform regulatory decision-making. Importantly, consistent with the findings of the EPA Human Studies Review Board (HSRB), which was asked to review some formaldehyde literature for EPA,[8] formaldehyde does not follow Haber's Law, and there is no meaningful difference in formaldehyde-induced sensory irritation regardless of whether the exposure is acute

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[4] Golden, R., *Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards*, Crit. Rev. in Toxic, 2011: 41(8): 672-721; available at: *https://www.tandfonline.com/doi/full/10.3109/10408444.2011.573467?role=tab&tab=permissions&aria-labelledby=reprints-perm&scroll=top*.

[5] Heck, et al., *Determination of formaldehyde in biological tissues by gas chromatography/mass spectrometry, Biomed Mass Spectrom*.1982 Aug;9(8):347-53; Heck, et al., *Formaldehyde (CH2O) concentrations in the blood of humans and Fischer-344 rats exposed to CH2O under controlled conditions*, Am Ind Hyg Assoc J. 1985, Jan;46(1): 1-3.

[6] Kimbell et al., *Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat*, Toxicol Appl Pharmacol. 1993 Aug;121(2):253-63.

[7] Lu et al., *A Review of Stable Isotope Labeling and Mass Spectrometry Methods to Distinguish Exogenous from Endogenous DNA Adducts and Improve Dose-Response Assessments*, 2022, Chem Res Toxicol. Available at: https://pubmed.ncbi.nlm.nih.gov/34910474/.

[8] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

or chronic.[9] Protecting for sensory irritation protects for all other adverse effects of formaldehyde (including nasal tumors) when a threshold-based mode of action (MOA) for nasal tumors is applied. The purpose of considering evidence in an MOA context is the recognition that chemicals initiate a series of biological responses in a dose-dependent and temporally related way. The (upstream) effects observed at low doses and early time points are plausibly linked to the (downstream) effects observed at high doses and later time points. This is well understood for formaldehyde, including for the MOA for nasal tumors.

The available scientific literature provides considerable evidence of an observed threshold for effects from formaldehyde exposure. In 2010, the World Health Organization (WHO) recognized that a threshold-based approach is appropriate for establishing indoor air quality guidelines for formaldehyde.[10] In 2018, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) also recognized a threshold for formaldehyde exposure when establishing its values for safe long-term exposure.[11]

Authoritative European Union scientific bodies have evaluated formaldehyde in the past 15 years, including the European Chemicals Agency (ECHA), the Scientific Committee on Occupational Exposure Limits (SCOEL), and the Committee on Risk Assessment (RAC).[12] Each of these authorities used a weight of the scientific evidence approach and considered all the available information, including information regarding endogenous and biogenic exposures. All these authorities agree that there is a threshold below which adverse effects, including nasopharyngeal cancer (NPC), do not occur. And all these authorities agree that this level is well above typical indoor and outdoor exposure levels.

The Department should not consider banning formaldehyde in consumer products when the concentrations in those products are lower than the concentrations naturally present in our own bodies and in the foods we eat. Any contrary action would be inconsistent with the Department's statutory obligations.

None of the studies and reviews described in this section are cited in the Draft Phase 2 Report.[13]

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[9] Golden, R., *Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards*, Crit. Rev. in Toxic, 2011: 41(8): 672-721; available at: https://www.tandfonline.com/doi/full/10.3109/10408444.2011.573467?role=tab&tab=permissions&aria-labelledby=reprints-perm&scroll=top.

[10] World Health Organization (WHO). 2010 Formaldehyde. In: Selected pollutants. WHO Guidelines for Indoor Air Quality. WHO, Regional Office for Europe, Copenhagen, Denmark, pp. 103-156.

[11] The French Agency for Food, Environmental and Occupational Health & Safety. (2018). Opinion on the revision of ANSES's reference values for formaldehyde: occupational exposure limits (OELs), derived no-effect levels (DNELs) for professionals, toxicity reference values (TRVs) and indoor air quality guidelines (IAQGs)

[12] EU, SCOEL/REC/125 Formaldehyde, Recommendation from the Scientific Committee on Occupational Exposure Limits, 2016, available at: https://op.europa.eu/en/publication-detail/-/publication/7a7ae0c9-c03d-11e6-a6db-01aa75ed71a1.

[13] From this point on, this comment is referring to *Appendix A. Citation List* which identifies the peer-reviewed science, studies, reports, and other sources of information used to support the Department's identification of priority chemicals. See Identification of Priority Chemicals Report to the Legislature Safer Products for Washington Cycle 2 Implementation Phase 1, May 2024, Available at: https://apps.ecology.wa.gov/publications/documents/2404025.pdf.

3. There is a Threshold-Like Dose Response for Nasal Tumor Formation in Rats, an Updated Mode of Action and Inconclusive Epidemiological Evidence

There is a wealth of scientific evidence supporting a threshold between formaldehyde exposure and NPC. In 2011, Lu et al. generated the first molecular dosimetry data using formaldehyde-specific DNA biomarkers and reported the formation of exogenous formaldehyde DNA adducts was highly non-linear.[14] And in 2019, Leng et al. detected endogenous but not exogenous adducts in rats exposed to low doses of formaldehyde by inhalation.[15] In 2020, the mode of action (MOA) framework for nasal tumors was updated by Thompson et al.[16] It was found that there are exposure concentrations below which there are no detectable biomarkers of exposure in rats. Finally, Marsh et al. analyzed (2014)[17] and re-analyzed (2016)[18] NPC mortality and formaldehyde exposure in one of ten factories reported in the 2004 follow-up of the National Cancer Institute (NCI) formaldehyde cohort study. The Marsh analyses found the NPC mortality and formaldehyde exposure in the one factory reported in the NCI study was neither consistent with the available data nor with other research findings based on this group of U.S. formaldehyde workers.

None of the studies described in this section are cited in the Draft Phase 2 Report.

4. There is a Lack of Biological Plausibility for a Causal Association Between Inhaled Formaldehyde and Lymphohematopoietic Cancers

The Department specifically references the National Toxicology Program's (NTP) conclusion of an association between formaldehyde exposure and leukemia. However, NTP's classification of formaldehyde as a "known human carcinogen" was issued without conducting a causation evaluation. In fact, NTP states this "only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives."[19]
Other authoritative bodies, particularly in the EU, have reached vastly different conclusions regarding formaldehyde and leukemia. The European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) found that "the epidemiology data do not show consistent findings across studies for leukemia rates" and "the lack of biological plausibility argue against formaldehyde as the cause of the increased rates".[20] Similarly the EU Scientific Committee on

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[14] Lu,K., B. Moeller, M. Doyle-Eisele, J. McDonald, & J. Swenberg (2011) Molecular Dosimetry of N2-hydroxymethyl- dG DNA adducts in rats exposed to Formaldehyde Chemical Research in Toxicology 24(2):159-161

[15] Leng, J., Liu C., Hartwell, J.H., Yu, R., Lai, Y., Bodnar, W.M., Lu, K., and Swenberg, J.A. (2019)."Evaluation of inhaled low-dose formaldehyde-induced DNA adducts and DNA–protein cross-links by liquid chromatography–tandem mass spectrometry." Archives of toxicology: 1-11

[16] Thompson, C. M., Gentry, R., Fitch, S., Lu, K., & Clewell, H. J. (2020). "An updated mode of action and human relevance framework evaluation for Formaldehyde-Related nasal tumors." Critical Reviews in Toxicology, 50(10), 919-952.

[17] Marsh, G., Morfeld, P., Collins, J., Symons, JM. (2014). Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. Journal of Occupational Medicine and Toxicology 9, no. 1: 1.

[18] Marsh, G., Morfeld, P., Zimmerman, S., Liu, Y., and Balmert, L. (2016). An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study." Journal of Occupational Medicine and Toxicology 11, no. 1: 1.

[19] NTP. 2010. Report on Carcinogens, Twelfth Edition. Introduction. p.3 Available at Report on Carcinogens. Twelfth Edition, 2011. | National Technical Reports Library - NTIS

[20] RAC (Risk Assessment Committee), 2012. Opinion Proposing Harmonised Clasification and Labelling at EU Level of Formaldehyde. European Chemicals Agency, Helsinki 30 November 2012

Occupational Exposure Limits (SCOEL) concluded, "there is no biological plausibility for an induction of human leukemia by formaldehyde exposure" and "systemic genotoxic action of inhaled FA is not likely".[21]

Lastly, there is extensive scientific literature that also does not support a causal association between formaldehyde and leukemia. For example, in 2020, Gentry et al.[22] critically evaluated the plausibility of the association between formaldehyde inhalation exposure and leukemia. Their analysis focused on the postulated MOA for leukemia following inhalation exposure to formaldehyde and the research relevant to the key events using the WHO/International Programme on Chemical Safety (IPCS) MOA framework. The authors concluded that none of the four postulated MOAs evaluated was biologically plausible, using the IPCS MOA framework, and the weight of evidence did not support the postulated MOAs. More recently, Vincent et al., 2024, conducted a systematic review focusing on the relationship between formaldehyde and LHP cancers, including myeloid leukemia.[23] This systematic review found "no credible explanation linking inhaled formaldehyde to LHP cancers, and no evidence of formaldehyde entering the bone marrow or blood when inhaled" and determined that causation is unlikely.

None of the studies described in this section, except for the NTP report, are cited in the Draft Phase 2 Report.

5. Typical Formaldehyde Exposures are Not Associated with Asthma

A number of reviews do not support the classification of formaldehyde as an asthmagen. In ECHA's 2019 substance evaluation report on formaldehyde, it was concluded that "a very limited number of case reports have been published on formaldehyde-related asthma but these data do not provide sufficient evidence that formaldehyde should be considered a risk factor for respiratory tract sensitization."[24] The National Academy of Sciences (NAS) reviewed asthma and indoor air exposures.[25] In this review, NAS only found limited or suggestive evidence of an association between formaldehyde exposure and exacerbations of asthma. In 2017, Golden and Holm evaluated the literature and found that studies reviewed incorrectly concluded that there was a significant positive association between formaldehyde exposure and childhood asthma.[26]

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[21] European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Klein, C., Nielsen, G., Johanson, G.et al., SCOEL/REC/125 formaldehyde – Recommendation from the Scientific Committee on Occupational Exposure Limits, Publications Office, 2017, https://data.europa.eu/doi/10.2767/399843

[22] Gentry, R., Thompson, C.M., Franzen, A., Salley, J., Albertini, R., Lu, K., and Greene, T. (2021). "Using mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia." Critical Reviews in Toxicology, 1-34

[23] M J Vincent, S Fitch, L Bylsma, C Thompson, S Rogers, J Britt, D Wikoff, *Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility*, Toxicological Sciences, 2024, kfae039, https://doi.org/10.1093/toxsci/kfae039.

[24] European Chemicals Agency (June 2019). Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for Formaldehyde. See: https://echa.europa.eu/documents/10162/cc0acabf-6e82-f2ed-5dbe-8058f48ce6c4

[25] National Academy of Sciences (NAS) (2000) Institute of Medicine (IOM). Clearing the Air: Asthma and Indoor Air Exposures. Washington, DC: National Academy Press.

[26] Golden, R., and Holm, S. (2017). Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies? Dose Response. Feb 15;15(1).

It is also important to recognize that the well-established declines in olfactory and trigeminal (chemesthetic) sensitivity with age and age-related diseases means a younger, healthier population (which is typically the demographic of participants in controlled exposure studies) will be most sensitive to the odor and irritancy of formaldehyde.[27] Other authoritative bodies have this same conclusion. The NAS found that, at exposure concentrations at or below 3 ppm, asthmatic individuals do not appear to be at greater risk of suffering airway dysfunction than non-asthmatic individuals.[28] The 2010 World Health Organization (WHO) evaluation concluded that there is no evidence indicating an increased sensitivity to sensory irritation to formaldehyde among people often regarded as susceptible.[29] In addition, chemosensory expert Dr. Pamela Dalton has reviewed numerous studies, controlled and observational, that included asthmatics and other sensitive individuals, and these studies do not show that asthma and other health conditions predispose individuals to be more sensitive to formaldehyde.[30] Thus, when it comes to formaldehyde, consistent with the findings of the EPA Human Studies Review Board (HSRB)[31] it is important to remember that a younger and generally healthier population will be the most sensitive. Thus, there is no disproportional effect on populations that are typically considered to be potentially exposed or susceptible subpopulations.

With regard to the reported associations between formaldehyde exposures and childhood or adult asthma risk, there remain a number of unanswered questions. In exploring possible mechanisms for formaldehyde-induced bronchoconstriction, Thompson and Grafstrom (2008) noted that "[t]he potential for formaldehyde to provoke asthma, hypersensitivity, and airway constriction in adults and children has received extensive attention over the years, yet data regarding these effects remain equivocal."[32] Although the hypothetical mechanism proposed by those authors may or may not lead to a better understanding of whether formaldehyde plays a causative role in asthma-related bronchoconstriction, at present the evidence suggests that asthma is neither caused nor exacerbated by low-level exposure (i.e., less than 1-2 ppm).[33]

Additional mechanistic support, as reported in multiple publications, explaining why asthmatics are not more sensitive to formaldehyde at environmentally relevant levels is the well documented effective scrubbing of low levels of formaldehyde in the upper airways below 3 ppm.[34] As a

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[27] See Dalton, P., comments to NAS 2022, PAF-20, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0107.

[28] NAS, *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants Volume 1*, 2007, at page 108, available at: https://nap.nationalacademies.org/download/11170#.

[29] World Health Organization (WHO) (2010): Regional Office for Europe. *WHO Guidelines for Indoor Air Quality: Selected Pollutants*. Copenhagen, Denmark: World Health Organization.

[30] Dalton, P, Comments to EPA on the Draft IRIS Formaldehyde Assessment, June 13, 2023, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0086 and https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613/comments.

[31] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

[32] Thompson, C. M. and R. C. Grafstrom (2008). *Mechanistic Considerations for Formaldehyde-Induced Bronchoconstriction Involving S-Nitroglutathione Reductase*. Journal of Toxicology and Environmental Health Part A [US CPSC] US Consumer Product Safety Commission 1982. Release # 82-005. Available from: 71: 244-248, available at: https://doi.org/10.1016/j.taap.2008.09.011.

[33] Noisel N, le Bouchard M, Carrier G. *Evaluation of the health impact of lowering the formaldehyde occupational exposure limit for Quebec workers*. Regul Toxicol Pharmacol. 2007;48:118–127.

[34] *See* for example, Schlosser PM, Lilly PD, Conolly RB, Janszen DB, Kimbell JS. *Benchmark dose risk assessment for formaldehyde using airflow modeling and a single-compartment DNA-protein cross-link dosimetry model to*

result, little formaldehyde at these concentrations reaches the mid- to lower airways where an asthmatic reaction may be triggered. The lack of sensitivity of asthmatics at these lower air levels in controlled human studies is consistent with expected patterns of absorption in the upper airways. While formaldehyde is clearly a sensory irritant at sufficient concentrations, its potential to cause or exacerbate asthma is far less certain, particularly at low exposure levels (<1-2 ppm). OSHA regulations state that "[c]oncentrations of above 5 ppm readily cause lower airway irritation characterized by cough, chest tightness, and wheezing."[35] It is also worth noting that there are no studies in which exposure to formaldehyde alone has been shown to cause or exacerbate asthma. Instead, studies that have reported this effect are all observational studies which have been confounded, to an unknown extent, by simultaneous co-exposures to other chemicals, many of which have been associated with exacerbating asthmatic symptoms.[36]

None of the studies or reviews described in this section are cited in the Draft Phase 2 Report.

6. Observational Studies are Not Best Available Science; Controlled Human Exposure Studies are the "Gold Standard"

Observational epidemiological studies, also known as ecological studies, seek to evaluate the association between the occurrence of a disease and an exposure. Conflicting results from observational epidemiological studies that look at the risks to daily life, such as coffee, alcohol, chocolate, hormones, or carbohydrates have provided a constant source of stress and angst for the general public. We often find that, when further evaluated in randomized control trials, the results are contradicted. This is because confounding due to the presence of other factors in the exposure environment is hard to control for, and the poor design of many observational studies does not allow for a full accounting of these external influences. It is well accepted that a randomized control study will always be preferred, and, although often difficult and expensive, controlled human exposure studies (also known as chamber studies) are the most reliable "gold standard" for evaluating cause and effect.

In a controlled human exposure study, subjects are known, exposures are known, and confounders are known and controlled. Because of the challenges, and potential ethical concerns associated with controlled human exposure studies, we often do not have data from them, and thus lesser quality epidemiological studies are used. In the case of formaldehyde, multiple high quality controlled human exposure studies exist and should be used.

When evaluating formaldehyde for the determination of occupational limits, other authoritative bodies have chosen to rely on controlled human exposure studies over observational epidemiological studies and in doing so relied upon sensory irritation effects as protective of all

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estimate human equivalent doses. Risk Anal. 2003;23:473–487; Kimbell JS, Gross EA, Joyner DR, Godo MN, Morgan KT. *Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat*. Toxicol Appl Pharmacol. 1993;121:253–263; Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB, Miller FJ. *Dosimetry modeling of inhaled formaldehyde: Binning nasal flux predictions for quantitative risk assessment*. Toxicol Sci. 2001;64:111–121; Overton JH, Kimbell JS, Miller FJ. *Dosimetry modeling of inhaled formaldehyde: The human respiratory tract.* Toxicol Sci. 2001;64:122–134; and, Garcia GJ, Schroeter JD, Segal RA, Stanek J, Foureman GL, Kimbell JS. *Dosimetry of nasal uptake of water-soluble and reactive gases: A first study of interhuman variability*. Inhal Toxicol. 2009;21:607–618.

[35] 29 C.F.R. § 1910.1048. Formaldehyde Appendix C.

[36] *See* comments submitted to the SACC from AF&PA, May 2024, available at https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

other non-cancer and cancer effects.[37] In 2017, ACGIH relied upon Lang et al., and in 2016, SCOEL relied on Mueller et al. and Lang et al. In 2010, for general population exposures, WHO also relied on controlled human exposure studies (Lang et al.), and in 2007, the NAS also recommended controlled human exposure studies when evaluating formaldehyde exposures in submarines.

The EPA HSRB also noted that the controlled chamber studies have "a preferred study design and greater scientific rigor than the observational studies."[38] As noted above, controlled human exposure studies provide great advantages over observational studies. In particular, the HSRB recommended relying on Mueller et al. and Lang et al., and particularly Lang et al. for deriving a point of departure consistent with the best available science and based on a weight of the evidence approach. The OPP Data Evaluation Records (DERs) for Mueller and Lang also concluded that both of these studies provide data for quantitative use for deriving a point of departure.[39]

These organizations evaluated the weight of the evidence and determined that the best science came from relying on studies where the populations, exposures, and confounders were controlled. The Department should similarly use the controlled human exposure studies for evaluating the occupational, consumer, indoor air, and ambient air scenarios.

None of the studies or reviews described in this section are cited in the Draft Phase 2 Report.

7. The Department's Reliance on an Observational Study for Asthma is Not Supported

The Department's reliance on the methodologically deficient 1990 observational study by Krzyanowski et al.[40] for its findings of decreased pulmonary function in children is misplaced and is not consistent with the best available science.[41] Detailed comments by independent experts have been provided to EPA and the Scientific Advisory Committee on Chemicals (SACC) on the weaknesses of this study.[42]

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[37] *See* Goyak and Holm (2024). *Sensory irritation and use of the best available science in setting exposure limits: Issues raised by a scientific panel review of formaldehyde human research studies.* Reg Tox Pharm., available at: https://doi.org/10.1016/j.yrtph.2024.105587; and Celanese comments, to EPA, Oct. 13, 2023, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0128.

[38] HSRB Final Report, Oct. 5, 2023, available at: https://www.epa.gov/system/files/documents/2023-10/july-2023-hsrb-report-woe-formaldehyde_0.pdf.

[39] *See* DERs for Lang et al. 2008 and Mueller et al. 2013, available at 42. DER Lang 2008 Draft Risk Evaluation for Formaldehyde and 43. DER Mueller 2013 Draft Risk Evaluation for Formaldehyde, and Debra Kaden presentation to the HSRB on Lang et al. and Mueller et al., available at: https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0106/attachment_3.pdf and https://downloads.regulations.gov/EPA-HQ-OPPT-2023-0613-0106/attachment_2.pdf.

[40] Krzyzanowski, M., Quackenboss, J. J., & Lebowitz, M. D. (1990). Chronic respiratory effects of indoor formaldehyde exposure. Environmental Research, 52(2), 117–125. https://doi.org/10.1016/S0013-9351(05)80247-6

[41] Washington State Department of Ecology, Technical Supporting Documentation for Priority Chemicals Safer Products for Washington Cycle 2 Implementation Phase 1, May 2024, Available at: https://apps.ecology.wa.gov/publications/documents/2404026.pdf

[42] *See* Comments submitted to the SACC, May 2024, from Dr. Dennis Paustenbach (P&A), Linda Dell (Ramboll), Dr. Stewart Holm (AF&PA) and Renee Kalmes and Dr. Pamela Dopart (E^{x}ponent), available at https://www.regulations.gov/docket/EPA-HQ-OPPT-2023-0613.

This flawed study was inexplicably assigned high confidence by the Integrated Risk Information System (IRIS) program. In support of this confidence rating, EPA describes the study as addressing confounders "including asthma status, smoking status, socioeconomic status, NO_2 levels, episodes of acute respiratory illness, and the time of day." However, there are significant transparency concerns with this study, which were also noted by the NAS in both its 2011 and 2023 reviews of the Draft Formaldehyde IRIS Assessments. Study characteristics are not fully reported, there is no information provided on NO_2 levels (even though the study says measurements were taken), readers cannot discern how the authors picked the preferred best model, the study design is unclear, and, although information on symptoms was collected, no information on the relationship between these symptoms and pulmonary function are presented. This was a cross-sectional study conducted over two weeks, where only two measurements of formaldehyde levels were taken for each participant, and four pulmonary function measurements were taken each day. However, the observations presented in the data tables represent, on average, only two measurements per day per person, not four measurements per day. Day-to-day and morning-to-night fluctuations in formaldehyde levels in indoor air were not accounted for. And, although EPA reports that confounding was addressed, in the final model used there was no adjustment for smoking status, NO_2, or episodes of acute respiratory illness. Finally, while the study also evaluated respiratory effects in adults, no effects in adults were associated with formaldehyde exposures.

Putting aside the weaknesses above, and other weaknesses that are not mentioned here, Krzyzanowski et al. is simply not reliable. The study's ability to determine causality specific to formaldehyde is weak at best. Dr. Dennis Paustenbach in his review refers to the point of departure derived from the study as "scientifically unsound"[43] due to the plethora of confounders that were not addressed, and Linda Dell in her review considers the study to be simply "uninformative."[44]

None of the reviews or studies described in this section, except Krzyanowski 1990, are cited in the Draft Phase 2 Report.

8. Consumer Exposure to Formaldehyde is Low and Adequately Regulated

The Department describes several potential exposures to formaldehyde including indoor and outdoor air as well as dermal exposure. There are a number of publications and reviews that demonstrate consumer exposure does not pose cancer risk. In a 2017 publication, Sheehan et al. evaluated formaldehyde concentrations in approximately 18,000 residences and found that formaldehyde emissions posed virtually no cancer risk.[45] The typical indoor exposure levels are between 16 and 32 ppb.[46] The WHO reviewed epidemiological studies from the NCI and concluded that "for purposes of indoor air guideline setting, that no excess nasopharyngeal

[43] Dr. Dennis Paustenbach (P&A) comments submitted to EPA SACC, May 2024, Available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0222

[44] Linda Dell (Ramboll) comments submitted to EPA SACC, May 2024, Available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0236

[45] Sheehan, P., Singhal, A., Bogen, K.T., MacIntosh, D., Kalmes, R.M., McCarthy, J. 2017. Potential Exposure and Cancer Risk from Formaldehyde Emissions from Installed Chinese Manufactured Laminate Flooring. Risk Analysis. 38(6): 1128-1142

[46] Salthammer, T., Mentese, S., & Marutzky, R. (2010). Formaldehyde in the indoor environment. Chemical Reviews, 110(4), 2536-72.

cancer was reported at a mean formaldehyde exposure at or below 1.25 mg/m3 [1,020 ppb] and with peak exposures below 5 mg/m3 [4,100 ppb]".[47] Taking the average indoor exposure levels of 16-32 ppb, which again is for all sources in the home, it is abundantly clear that average indoor air exposures fall very far below the threshold for cancer risk. Lastly, although dermal exposure to formaldehyde-containing liquid is possible for some applications, routine skin contact is not likely. This is because the irritating and absorptive properties preclude ongoing skin contact and systemic effects.[48] Further, NIOSH states that "data on in vivo toxicokinetics in animals suggest that formaldehyde has limited potential to be absorbed through the skin (i.e., percent absorption of less than 10%)."[49]

None of the studies and reviews described in this section, except Salthammer 2010, are cited in the Draft Phase 2 Report.

As highlighted below, there are federal agencies that have reviewed and, in some cases, regulated formaldehyde.

- In December 2016, the Environmental Protection Agency (EPA) issued a final rule to implement the Formaldehyde Emission Standards for Composite Wood Products Act. This rule includes formaldehyde emission standards applicable to hardwood plywood, medium density fiberboard (MDF), and particleboard, and finished goods containing composite wood products, that are sold, supplied, offered for sale, or manufactured (including imported) in the United States. EPA worked with the California Air Resources Board to ensure the final federal rule set emission levels consistent with California's requirements for composite wood products. [50]
- The Department of Housing and Urban Development (HUD) has standards in place that limit formaldehyde emissions from wood products used in manufactured housing. HUD also requires that all such products be certified by a nationally-recognized testing laboratory to verify compliance with HUD's formaldehyde emissions limits. [51]
- The Consumer Product Safety Commission (CPSC) has extensively studied formaldehyde emissions in the home environment and has not recommended additional regulation or limits based on the available science. [52]
- The Food and Drug Administration (FDA) has reviewed the safety of formaldehyde and approved its use as an indirect food additive in a number of materials having contact with food. [53]

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[47] World Health Organization (WHO). 2010 Formaldehyde. In: Selected pollutants. WHO Guidelines for Indoor Air Quality. WHO, Regional Office for Europe, Copenhagen, Denmark, pp. 103-156.
[48] ECHA (2019). Worker exposure to formaldehyde and formaldehyde releasers. Available at: https://echa.europa.eu/documents/10162/13641/investigationreport_formaldehyde_workers-exposure_final_en.pdf/ac457a0c-378d-4eae-c602-c7cd59abc4c5
[49] NIOSH Skin Notation Profiles: Formaldehyde/Formalin, April 2011. Available at NIOSH Skin Notation Profiles: Formaldehyde/Formalin | NIOSH | CDC
[50] EPA, Formaldehyde Emission Standards for Composite Wood Products, available at: https://www.epa.gov/formaldehyde/formaldehyde-emission-standards-composite-wood-products
[51] HUD, 24 CFR 3280 -Manufactured Home Construction and Safety Standards, available at: https://www.govinfo.gov/app/details/CFR-2010-title24-vol5/CFR-2010-title24-vol5-part3280
[52] CPSC, An Update on Formaldehyde, available at: https://www.cpsc.gov/s3fs-public/An-Update-On-Formaldehyde-725_0.pdf
[53] FDA, Inventory of Food Contact Substances Listed in 21 CFR: Formaldehyde, available at: https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives&id=FORMALDEHYDE

- Formaldehyde-releasing chemistries are registered as pesticides by the US EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and by the Washington Department of Agriculture. While EPA's Registration Review case for formaldehyde releasers is currently under review, these chemistries have been assessed by EPA previously and found to pose no unreasonable risk to human health or the environment from their use in cleaning and household products.[54]

The state of Washington has already taken steps to regulate formaldehyde in certain products. The Toxics Free Cosmetics Act was signed into law on May 15, 2023, and bans formaldehyde and formaldehyde releasers used in cosmetics.

Additionally, ECHA recently (July 2023) completed its review of formaldehyde and formaldehyde releasers and released its final restriction proposal. As part of the restriction process, ECHA reviewed all sources of exposure to formaldehyde from formaldehyde and formaldehyde releasers and did not find that the use in cleaning and household products posed a risk needed further restriction. Specifically, ECHA noted in the restriction, "Based on available literature and the outcome of the exposure estimation, the Dossier Submitter concluded that **human health risks from formaldehyde release from mixtures for consumer use are adequately controlled**."[55]

Further, in the Annex XV restriction report, ECHA notes, "The cleaning and detergents industry has confirmed that formaldehyde may be present in the mixture in concentrations not exceeding 200 ppm (0.02%). Furthermore, a voluntary industry agreement was signed with the intention to not exceed the WHO guideline value of formaldehyde in indoor environments (0.1 mg/m3) from the use of cleaning products."[56]

Given the strong data supporting that exposure to formaldehyde from the use of formaldehyde releasers as preservatives in cleaning and household products is minimal, it is unclear why the Department has selected these chemistries and use patterns as a priority product in the Draft Report. We encourage the Department to defer to the U.S. EPA, ECHA, and other regulatory agencies that are assessing a significant volume of data specific to these chemistries' uses and use patterns to determine whether there is a risk to public health or the environment.

9. Formaldehyde is Currently Being Evaluated by EPA

Formaldehyde is undergoing review by the Office of Pesticide Programs (OPP) under FIFRA as part of the Registration Review process while concurrently undergoing review by the Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA) risk evaluation process. Formaldehyde was designated as a high priority chemical for risk evaluation under TSCA in December of 2019. The draft TSCA risk evaluation was issued in March 2024 and is expected to be finalized in December 2024. The FIFRA Registration Review Draft Risk

[54] See EPA Reregistration Eligibility Decision (RED) for Bronopol Fact Sheet, available at: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-216400_1-Oct-95.pdf
[55] COMMISSION REGULATION (EU) 2023/1464 of 14 July 2023 amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council as regards formaldehyde and formaldehyde releasers. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R1464
[56] https://echa.europa.eu/documents/10162/ee418b46-92cc-8db2-de97-5c7599df763c

Assessment for Formaldehyde and Paraformaldehyde was issued in April 2024 and is expected to be finalized along the same timeline as the TSCA risk evaluation. When final, the respective risk evaluations will be used to inform potential future regulations under TSCA and FIFRA.

The OPP assessment focuses on the pesticidal uses of formaldehyde and paraformaldehyde registered under FIFRA. For instance, the following is a summary of registered pesticidal uses of formaldehyde for materials preservative (in can): air fresheners, automotive products, waxes and automotive polishes, car washes; polishes for floors and furniture, shoe polishes, carpet cleaners and spot removers, fabric softeners, spray starch, hand and automatic dish detergents, liquid laundry detergents, hand cleaners, moist sponges and towelettes, household cleaners, industrial cleaners, liquid hand soaps, oil and grease removers, waterless hand cleaners, raw materials for cleaning products, surfactants and silicone emulsions.[57]

The scope of the TSCA risk evaluation includes any potential consumer exposures from a broad range of products, including: floor coverings; foam seating and bedding products; cleaning and furniture care products; furniture & furnishings including stone, plaster, cement, glass and ceramic articles; metal articles; or rubber articles; fabric, textile, and leather products not covered elsewhere (clothing); water treatment products; laundry and dishwashing products; adhesives and sealants; paint and coatings; construction and building materials covering large surface areas, including wood articles; construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles; machinery, mechanical appliances, electrical/electronic articles; other machinery, mechanical appliances, electronic/electronic articles; automotive care products; lubricants and greases; fuels and related products; lawn and garden products; paper products; plastic and rubber products; toys, playground, and sporting equipment; arts, crafts, and hobby materials; ink, toner, and colorant products; and photographic supplies.

The FIFRA and TSCA risk evaluations and any subsequent risk management will thus very likely consider any applications the Department would evaluate for formaldehyde, if designated as a priority chemical under its program. Therefore, any regulatory action the Department sought to impose restricting or prohibiting the presence of formaldehyde in products could be preempted pursuant to 15 U.S.C. § 2617.

10. Recent Reviews and Publications Relevant to Formaldehyde

The Draft Phase 2 Report fails to fully incorporate the latest peer reviews and publications on formaldehyde.

Four important reviews have been released evaluating EPA's formaldehyde science that are relevant to the Department's evaluation of formaldehyde:

- Most recently, in August 2024, the EPA SACC released its final report and meeting minutes on their peer review of the draft risk evaluation of formaldehyde describing fundamental flaws that demonstrate failures to meet TSCA's scientific standards and process requirements.

[57] EPA FIFRA Registration Review Draft Risk Assessment for Formaldehyde and Paraformaldehyde; April 2024, Available at: https://www.regulations.gov/document/EPA-HQ-OPP-2015-0739-0011

- In August 2023, the NAS Review of EPA's 2022 Draft Formaldehyde Assessment released a report describing its review of the adequacy and transparency of EPA's methods in the 2022 Draft IRIS Formaldehyde Assessment. The Department must recognize the limited nature of this NAS review. The NAS committee was not charged with commenting on the full body of literature relevant to the hazards and risks of formaldehyde, nor was it charged with reviewing alternative scientific opinions.[58] The NAS review was additionally compromised due to procedural shortcomings and FACA violations including a lack of fair balance on the committee[59] and because of appearance of a lack of impartiality or independence.[60]

- Also in August 2023, the EPA HSRB approved a report that described its review of the ethics and science related to four studies that EPA used in a weight-of-evidence evaluation for acute sensory irritation resulting from formaldehyde exposure.

- In 2011, a National Research Council (NRC) committee reported numerous still-relevant recommendations of a similar draft IRIS assessment. ACC has previously compiled these recommendations and explained in detail why they are legally required to be incorporated by EPA.[61] In addition, the 2022 NAS Committee acknowledged that "The present committee did not review specific changes in the 2022 Draft Assessment against the recommendations in the 2011 NRC report…"

Considering the limited nature of the 2022 NAS committee charge, and that the 2023 NAS report states that the committee "was not charged with…. reviewing alternative opinions of EPA's assessment," it is troubling that this NAS review was the only one cited in the Draft Phase 2 Report. We urge the Department to fully consider the other peer reviews referenced in this section.

Additionally, just this year, several important peer reviewed publications have been published that are highly relevant.

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[58] ACC has provided information to NASEM and EPA noting that over 100 peer-reviewed scientific studies were excluded from the Draft IRIS Assessment. Because NASEM was not asked to comment on excluded information and was not asked to comment on alternative scientific information, none of this information was considered by NASEM during its peer review. Those letters are available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0438-0067 and https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103 (see Appendix A). The list of excluded studies was also provided to the SACC and EPA on May 3, 2024, available at pages 23-33: ACC Formaldehyde Panel Comments for May 3, 2024 SACC Meeting - American Chemistry Council.

[59] *See* for example, ACC Comments to NASEM on Committee Composition, Aug. 25, 2022; ACC Letter to NASEM on Information Requests, Sept. 9, 2022; and NASEM Response to ACC on Information Gathering Session Request Mar. 6, 2023, all available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0126.

[60] ACC, Comments to NASEM on Committee Composition, Aug. 25, 2022, available at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2023-0613-0126.

[61] ACC Letter to EPA Administrator Regan, March 10, 2022, Re: National Academies of Sciences, Engineering, and Medicine (NASEM) Review of EPA's 2022 Draft Formaldehyde Assessment, Available at: https://www.americanchemistry.com/content/download/10668/file/Formaldehyde-Panel-Follow-Up-Letter-to-EPA-031022.pdf.

- Vincent, Melissa J., Seneca Fitch, Lauren Bylsma, Chad Thompson, Sarah Rogers, Janice Britt, and Daniele Wikoff. "Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility." *Toxicological Sciences* (2024). Available at: https://doi.org/10.1093/toxsci/kfae039.
    - Vincent et al., 2024, conducted a systematic review focusing on the relationship between formaldehyde and LHP cancers, including myeloid leukemia. This systematic review found "no credible explanation linking inhaled formaldehyde to LHP cancers, and no evidence of formaldehyde entering the bone marrow or blood when inhaled" and determined that causation is unlikely.

- Goyak, Katy, and Stewart Holm. "Sensory irritation and use of the best available science in setting exposure limits: Issues raised by a scientific panel review of formaldehyde human research studies." *Regulatory Toxicology and Pharmacology* (2024): 105587. Available at: https://doi.org/10.1016/j.yrtph.2024.105587.
    - Goyak and Holm, 2024, highlight that formaldehyde short-term exposure limits often protect against sensory irritation, scientific panels consistently recommend no adjustment for exposure duration, scientific panels consistently recommend no adjustment for human variability, and scientific consensus should be considered in the upcoming TSCA risk evaluation.
    - Update to the paper, reflecting the final IRIS assessment and draft TSCA risk evaluation, presented in a poster session at the Society for Risk Analysis conference, Dec 2024, available at: Comparing Risk Science Choices Underpinning Formaldehyde Exposure Levels Established by Independent Regulatory and Advisory Bodies - American Chemistry Council

- Lauer, Daniel J., Anthony J. Russell, Heather N. Lynch, William J. Thompson, Kenneth A. Mundt, and Harvey Checkoway. "Triangulation of epidemiological evidence and risk of bias evaluation: A proposed framework and applied example using formaldehyde exposure and risk of myeloid leukemias." *Global Epidemiology* 7 (2024): 100143. Available at: https://doi.org/10.1016/j.gloepi.2024.100143.
    - Lauer et al., 2024 developed a triangulation framework and applied it to occupational formaldehyde exposure and risk of myeloid leukemia and found that "most reported epidemiological results do not demonstrate statistically significant associations between occupational exposure to formaldehyde and risk of ML, AML or CML."

- Salthammer, Tunga. "The reliability of models for converting formaldehyde emissions from wood-based materials to different environmental conditions." *Building and Environment* 247 (2024): 111041. Available at: https://doi.org/10.1016/j.buildenv.2023.111041.
    - Salthammer 2024 compares and evaluates empirical models for the conversion of formaldehyde concentrations, presents parameters for the statistical prediction of formaldehyde concentrations, finds that a simple linear conversion of chamber concentrations for exposure assessments is not possible, and reports that tolerance limits of test chamber settings cause uncertainties that cannot be neglected.

- Cox Jr, Louis A., William J. Thompson, and Kenneth A. Mundt. "Interventional probability of causation (IPoC) with epidemiological and partial mechanistic evidence: benzene vs. formaldehyde and acute myeloid leukemia (AML)." *Critical Reviews in Toxicology* (2024): 1-38. Available at: https://www.tandfonline.com/doi/full/10.1080/10408444.2024.2337435
    - Cox et al., 2024 concludes that "no causal pathway leading from formaldehyde exposure to increased risk of AML was identified, consistent with much previous mechanistic, toxicological and epidemiological evidence."

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The Panel urges the Department to consider the wealth of scientific information and reviews described in these comments when considering its final designation of priority chemistries under the Safer Products program. It is also important for the Department to consider existing and potential future regulations for formaldehyde during this prioritization exercise so that Department resources can be effectively used to protect consumer and environmental health. Please feel free to contact me at sahar_osman-sypher@americanchemistry.com or 202-249-6721.

Sincerely,

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Chemical Products & Technology Division
American Chemistry Council
On Behalf of the ACC Formaldehyde Panel